REMARKS

Claims 1, 4, 7, 8 and 10-13 and 15-19 are pending.

Applicants herein Request Continued Examination (RCE) to accompany this Response.

Applicants thank the Examiner for indicating that claims 7 and 8 are allowed.

Applicants acknowledge the Examiner's rejection of claims 1, 4, 10-13 and 15 under 35 U.S.C. § 112 ¶1 for alleged ***new matter*** relating to the recitation of "coordinately methylated contiguous CpG island sequences that comprise SEQ ID NO:36 [or 37]." Applicants note, and have assumed for purposes of the present response, that the Examiner's rejection was likely intended to be of claims 1, 4, 13 and 15, based on the asserted grounds and pending claims. Applicants respectfully traverse this rejection, but have nonetheless made amendments to obviate this rejection.

Applicants acknowledge the Examiner's maintained rejection of claims 1, 4, 13 and 15, under 35 U.S.C. § 112 ¶1, based on alleged lack of ***written description*** for "coordinately methylated contiguous CpG island sequence that comprise SEQ ID NO:36 or 37. Applicants respectfully traverse this rejection.

Applicants acknowledge the Examiner's maintained rejection of claims 1, 4, 13 and 15 under 35 U.S.C. § 112 ¶1, based on alleged lack of ***enablement***. Applicants have amended claims 7 and 10, but respectfully traverse this rejection with respect to the other claims.

Applicants acknowledge the Examiner's rejection of claims 1, 4, 13 and 15, and 16-19, under 35 U.S.C. § 112 ¶2 based on alleged ***indefiniteness*** with respect to recitation of "coordinately hypermethylated," and the absence of a "linking" phrase, respectively. Applicants respectfully traverse this rejection, but have nonetheless made clarifying amendments to obviate the rejections.

No new matter has been added.

Alleged New Matter

The Examiner has rejected claims 1, 2, 4, 7, 8 and 10-15 under 35 U.S.C. § 112 ¶1 for alleged new matter relating to applicants' recitation of "coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO:36."

Specifically, the Examiner urges that the concept of "coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO:36" does not appear to be part of the originally filed invention (Office action of 08 November 2005, at page2). Applicants respectfully traverse this rejection.

Specifically, the specification at page 7, ll. 19-23 teaches (in reference to Tables I & II) that 55 out of the 103 nucleic acid sequences (including SEQ ID NOS:36 and 37) correspond to CpG islands or portions of CpG islands. Additionally, the specification at page 8, ll. 12-22 teaches that the "methylation **state** of **a portion of a CpG island is generally representative of the island as a whole**," and that the present invention therefore further encompasses CpG islands that are **associated contiguously** with the respective 55 sequences (including SEQ ID NOS:36 and 37). Therefore, the specification teaches that the methylation state of a CpG dinucleotide in one part of a contiguous CpG island is representative of the state of a CpG dinucleotide in another part of the same contiguous CpG island. As defined in the Webster dictionary, coordinate means: "to put in the same order or rank"; "to bring into common condition (harmonize)"; "to act together in a smooth concerted way"; etc. Applicants have thus used the work coordinate consistent with the instant teachings and its dictionary usage, and even more significantly, consistent with the art-recognized description of methylation state regulation in the context of CpG island methylation.

Additionally, as already present in the record, the instant specification teaches (*e.g.*, at page 10 line 12 to page 11, line 3; see also Definitions) that hypermethylation refers to the methylation states corresponding to an *increased* presence 5-methylcytosine ("5-mCyt") at one or a plurality of CpG dinucleotides within a DNA sequence of the test sample, relative to the amount of 5-mCyt found at corresponding CpG dinucleotides within a normal control DNA sample. Moreover, the specification teaches that the CpG dinucleotides of certain CpG islands are hypermethylated (see Table 2, hypermethylated CpG islands (including SEQ ID NOS:36 and 37)), and therefore it follows that the specification teaches that the CpG dinucleotides of certain CpG islands (including SEQ ID NOS:36 and 37) are coordinately hypermethylated.

Applicants have nonetheless amended claims 1 and 13 to recite "SEQ ID NO:36 [or SEQ

ID NO:37 in the case of claim 13] and a contiguous CpG island sequence that comprises SEQ ID NO:36 [or SEQ ID NO:37 in the case of claim 13], wherein the CpG island sequence is a contiguous sequence of about 0.2 to about 1 kb in length that satisfies the criteria of having both a frequency of CpG dinucleotides corresponding to an Observed/Expected Ratio >0.6, and a GC Content >0.5, and wherein the methylation state of a CpG dinucleotide in SEQ ID NO:36 [or SEQ ID NO:37 in the case of claim 13] is representative of the state of the CpG dinucleotides in the CpG island."

Support for recitation of "comprising" is found in the statement that the "methylation state of a **portion** of a CpG island is generally representative of the island as a whole; that is, the disclosure teaches that the hypermethyled SEQ ID NOS of Table 2 are comprised within (portion of) larger CpG islands, and that the the methylation state of a CpG dinucleotide in one part of a contiguous CpG island is representative of the state of a CpG dinucleotide in another part of the CpG island (coordinately methylated).

Applicants, therefore, respectfully request withdrawal of this rejection, based on applicants' above described amendments to independent claims 1 and 13.

Rejections under 35 U.S.C. § 112, ¶1

Written description:

The Examiner has maintained the rejection of claims 1, 4, 13 and 15, under 35 U.S.C. § 112 ¶1, based on alleged lack of written description for "contiguous CpG islands that comprise of SEQ ID NO:36 and 37.

Specifically the Examiner urges (citing The Regents of the University of Calif. v. Eli Lilly) that a generic statement defining a genus of nucleic acids by function is not enough to provide adequate written description (Office Action of 08 November 2005 at page 4).

However, in the present case applicants do not merely define a genus by functional activity. Specifically, the specification at page 5 and 8 teaches a formula; namely, "a CpG island sequence associated with a particular SEQ ID NO sequence of the present invention is that contiguous sequence of genomic DNA that encompasses at least one nucleotide of the particular SEQ ID NO sequence, and satisfies the criteria of having both a frequency of CpG dinucleotides corresponding to an Observed/Expected Ratio >0.6), and a GC Content >0.5." Physical properties and structure are also implicit within this definition, because the definition absolutely requires that

the associated sequence is contiguous with the portion of the CpG island. Contrary to the Examiner's urging, the recited genera (CpG island sequences comprising SEQ ID NO:36 [or 37]) are not merely defined by functional language, but rather are explicitly adequately defined by the core SEQ ID NO:36 sequence and the recited formula describing the larger CpG island. Therefore, the larger genomic CpG island is adequately defined and described by the core sequence and the formula.

Applicants point out that the Examiner's own example (see Office Action page 5):

**********(SEQ ID NO:36)*******(CpG)******

Illustrates that applicants' written description is adequate and commensurate in scope with the instant claims, because it has enabled the Examiner to present a species of applicants claimed genus, based on the core SEQ ID NO:36 and applicants CpG island formula. Additionally, as taught by applicants, and as recognized by the Examiner in presenting this example, the CpG dinucleotide sequences are the precise defined sequences that are assayed, regardless of their position withing the larger CpGisland, in determining methylation state.

Public policy considerations. Applicants are entitled to claims that are commensurate in scope not only with what applicants have specifically described and exemplified, and with that which one of skill in the art could obtain by virtue of that which the applicants have disclosed. In this instance, applicants have disclosed and taught portions of larger CpG islands, and importantly, have defined these larger CpG islands by applicants' formula. Applicants are the first to identify and recognize the recited utilities of these defined CpG islands.

It is unfair and unduly limiting and contrary to the public policy upon which the patents laws are based to require applicants to limit the claims to the exact sequences exemplified, when the application clearly teaches how to make and use nucleic acid sequences that contain the core SEQ ID NOS:36 and 37 sequences. See, for example, *In re Goffe*, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

> for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts."

The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the disclosure. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions. *In re Sus and Schafer*, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

If applicants are required to limit the claims as suggested by the Examiner, then those of skill in the art can, by virtue of the teachings of this application, readily prepare markers from the respectively larger CpG islands, thereby practicing what is disclosed in the application, but avoiding infringing such limited claims. The instant application provides a broader disclosure; and having done so, places the public in possession of such knowledge. Having provided this disclosure, it permits others to benefit therefrom. Those of skill in the art should not be permitted to practice what is taught in the application, but avoid infringing the claims. To permit that is simply not fair. Small early stage companies can ill-afford to dedicate their innovations to the public.

Applicants, therefore, respectfully request withdrawal of the Examiner's rejection of claims 1, 4, 13 and 15, under 35 U.S.C. § 112 ¶1, based on alleged lack of written description.

Further Rejections under 35 U.S.C. § 112, ¶1

Enablement:

The Examiner has maintained rejections of claims 1, 4, 13 and 15 under 35 U.S.C. § 112 ¶1, based on alleged lack of enablement.

Specifically, the Examiner urges (see Office Action page 10) that the specification has not taught "a predictable correlation between [cancer and] nucleic acids which are coordinately methylated contiguous CpG island sequences that comprise SEQ ID NOS:36 and 37," and "therefore, it is unpredictable that coordinately methylated contiguous CpG island sequences that comprise SEQ ID NOS:36 and 37 are indicative of cancers absent unpredictable and undue experimentation." Additionally, citing Toyota et al., the Examiner urges that "the art does not support the idea that all contiguous CpG islands are associated with cancer...." The Examiner urges that Toyota teaches a detailed analysis of CpG islands within the CACNA1G gene, stating that Toyota teaches "eight regions, each behaving differently" (regions 1 and 2 being concordant, regions 5, 6 and 7 behaving differently than regions 1-3, and regions 4, and 8 behaving differently again). The Examiner thereby concludes that "with respect to hypermethylation in cancer, the CpG region upstream of CACNA1G appears to behave independently" (citing page 4538, col. 1), and "therefore, since the art provides examples where CpG islands act in predictable ways

(applicant) and examples where CpG islands act independently [Toyota, as construed by the Examiner], it is unpredictable whether the instant CpG islands act in a predictable or independent manner," and "therefore, it is unpredictable that coordinately hypermethylated contiguous regions comprising SEQ ID NOS:36 and 37 are associated with cancer" (Office Action of 08 November 2005 at page 8).

Applicants respectfully traverse this rejection, because the Examiner has misconstrued the teachings of Toyota, which actually support applications position.

First, applicants reaffirm and reassert the Declaration of Dr. Cathy Lofton Day, already of record, and which will therefore not be reiterated herein.

Second, we are in agreement with the Examiner that Toyota teaches "examples where CpG islands act independently." However, that is not the relevant question here. The relevant question is whether the CpG dinucleotide sequences within a given CpG island behave coordinately. Here, the teachings of Toyota are in agreement with the applicants currently recited claims.

Specifically, Toyota initially describes/defines a large 4Kb region, based on a definition of having a GC content of 0.67; CpG/GpC ration of 0.78; and a total of 305 CpG sites in a 4-kb region (Toyota at pate 4536 column 2 middle of 1st full para), and divides this 4kb region into 8 subregions. However, Toyota notes that this region is considerably larger that typical CpG islands (Toyota at page 4537, column 2, 1st full para), and he explicitly concludes that "with regards to hypermethylation in cancer, the CpG-rich region upstream of CACNA1G appears to be composed of two CpG islands that behave independently" (MINT31 regions 1 and 2 corresponding to the upstream CpG island 1; the 5' regions 5-7 of CACNA1G in the downstream CpG island 2; and regions 3, 4 and 5 between CpG island 1 and 2, behaving differently. Toyota concludes (page 4540, at end of carryover para) that "methylation of MINT 31 appears to be independent of methylation of CACNA1G, suggesting that they are two distinct CpG island regulated by different mechanisms." Significantly, therefore, Toyota teaches that while different CpG islands within a gene area can behave differently or independently, the subregions within a given CpG island, for example regions 1 and 2 of island 1 and regions 5-7 of island 2, behave coordinately

and define the behavior of the CpG island which comprises the subregions.

Therefore, Toyota like the vast bulk of art in this area, is fully consistent with the teachings of the present invention which teach that the CpG dinucleotides within a given contiguous CpG island are coordinately methylated.

The instant specification has taught that a predictable correlation exists between hypermethylation of SEQ ID NOS:36 and 37 and cancer, and further teaches coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NOS:36 or 37. Therefore, it follows that the instant specification teaches that hypermethylated contiguous CpG island sequences that comprise SEQ ID NOS:36 or 37 are indicative of cancers.

Moreover, given the instant teachings and the state of the art, and fully consistent with Toyota cited by the Examiner, applicants contend that it would not entail undue experimentation to determine whether a CpG dinucleotide of the contiguous CpG islands that respectively comprise SEQ ID NO:36 or 37 is coordinately methylated with a CpG of SEQ ID NO:36 or 37. This is precisely what would be expected as described above, and in view of Toyota cited by the Examiner. Such a CpG island is readily identifiable and analyzable because it is structurally defined as being contiguous to applicant's disclosed SEQ ID NOS:36 or 37, and is further defined and describe by applicant's formula describe herein above. The level of skill in the art is high, and given the instant teachings and those of the art, isolation of such a CpG island sequence from a cancer tissue and determining the methylation state of one or more CpG residues therein relative to a control, could be done by one of ordinary skill in the art in a matter of a few days or a week using standard DNA manipulation methods and methylation assays available at the time of filing of the present application.

In light of the scope of the claims, the teachings in the specification, the presence of specific working examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in this art, and the predictability of the subject matter, it would not require undue experimentation for a person of skill in the art to practice the invention as claimed.

Therefore, the specification is enabling for making and using the full scope of the claimed subject matter.

Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 112 ¶2

The Examiner has rejected claims 1, 4, 13, 15 and 16-19, under 35 U.S.C. § 112 ¶2, based on alleged indefiniteness. with respect to recitation of "coordinately hypermethylated."

Specifically, with respect to claims 1, 4, 13 and 15, the Examiner asserts that it is unclear what is meant by "coordinately hypermethylated" (*e.g.*, whether is refers to the amount or location) and how this definition is related to hypermethylation (Office action of 08 November 2005 at page 15).

Claims 1, 4, 13 and 15. As described in detail above with respect to the Examiner's New Matter-based rejection, independent claims 1 and 13 have been amended to recite "SEQ ID NO:36 [or SEQ ID NO:37 in the case of claim 13] and a contiguous CpG island sequence that comprises SEQ ID NO:36 [or SEQ ID NO:37 in the case of claim 13], wherein the CpG island sequence is a contiguous sequence of about 0.2 to about 1 kb in length that satisfies the criteria of having both a frequency of CpG dinucleotides corresponding to an Observed/Expected Ratio >0.6, and a GC Content >0.5, and wherein the methylation state of a CpG dinucleotide in SEQ ID NO:36 [or SEQ ID NO:37 in the case of claim 13] is representative of the state of the CpG dinucleotides in the CpG island."

Additionally, as already of record, the instant specification teaches (*e.g.*, at page 10 line 12 to page 11, line 3; see also Definitions) that hypermethylation refers to the methylation states corresponding to an *increased* presence 5-methylcytosine ("5-mCyt") at one or a plurality of CpG dinucleotides within a DNA sequence of the test sample, relative to the amount of 5-mCyt found at corresponding CpG dinucleotides within a normal control DNA sample. Moreover, the specification teaches that the CpG dinucleotides of certain CpG islands are hypermethylated (see Table 2, hypermethylated CpG islands (including SEQ ID NOS:36 and 37)), and therefore it

follows that the specification teaches that the CpG dinucleotides of certain CpG islands (including SEQ ID NOS:36 and 37) are coordinately hypermethylated.

Claims 16-19. Applicants have amended claims 16 and 18 to recite "wherein hypermethylation of SEQ ID NO:36 [claim 16; or SEQ ID NO:37 (claim 18)] is indicative of breast cancer [claim 16] or of prostate, breast or colon cancer [claim 18]."

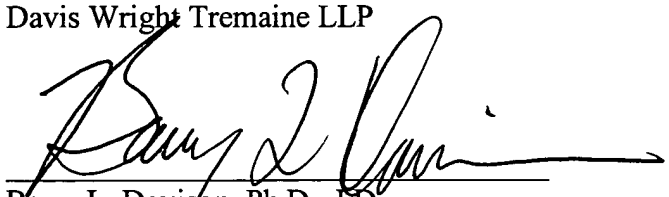
Applicants respectfully request that the rejection be reconsidered and withdrawn.

Conclusion

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration of the claimed invention, entry of the present responsive Amendment and allowance of all pending claims.

Respectfully submitted,

Davis Wright Tremaine LLP



Barry L. Davison, Ph.D., J.D.
Attorney for Applicant
Registration No. 47,309

Davis Wright Tremaine LLP
2600 Century Square
1501 Fourth Avenue
Seattle, Washington 98101-1688
Telephone: 206-628-7621
Facsimile: 206-628-7699